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TO: USPTO
Examiner Chukwuma O. Nwaonicha; Art Unit 1621

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FROM: Ronald J. Corbett

RE: Patent No. 7,012,140 issued March 14, 2006
Attorney Docket No.:UTAD-0004

DATE: August 10, 2006

PAGES: 16 (including cover page)

Certificate
AUG 11 2006
of Correction

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facsimile transmittal (pp.1);
Certificate of Correction Transmittal Letter (pp.6); and
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DOCKET NO. UTAD-0004

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PATENT

AUG 10 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Registered Patent No. 7,012,140 of:

A. Dean Sherry, Mark Woods and Zoltan Kovacs

Issued: March 14, 2006

Filed: July 14, 2003

Serial No.: 10/619,362

For: SELECTION OF COORDINATION GEOMETRY TO ADJUST WATER
EXCHANGE RATES OF PARAMAGNETIC METAL ION-BASED
MACROCYCLIC CONTRAST AGENTS

Group: 1621

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450I hereby certify that this correspondence is being facsimile transmitted to the Patent and
Trademark Office (Fax No. (571) 273-8300) on August 10, 2006Marty Balke
Printed or typed name of person signing the certificateMarty Balke
Date of Mailing Signature of person mailing

Sir:

CERTIFICATE OF CORRECTION TRANSMITTAL LETTER

AUG 11 2006

The following clerical or typographical errors were noted in Column 4, lines 14-17:

FIGURE 3A and FIGURE 3B illustrates exemplary ^1H NMR spectra of $[\text{Eu}(\text{S-RRRR-NO}_2\text{BnDOTMA})]^-$ $[\text{Eu}(\text{S-RRRR-NO}_2\text{BnDOTMA})]$ and $[\text{Eu}(\text{S-SSSS-NO}_2\text{BnDOTMA})]^-$, respectively, produced according to the present; and

The following clerical or typographical errors were noted in Column 5, lines 60-67 through and including Column 6, lines 1-3:

For example, when the three or more pendant arm carbon atoms C' have Δ orientations and the chirality of the one or more R^6 -substituted ring carbons is selected such that the macrocyclic ring has an identical ($\delta\delta\delta\delta$) orientation, then the tetraazacyclododecane ligand has a capped twisted square antiprism configuration. Or, when the three or more pendant arm carbon atoms C' have Λ orientations and the chirality of the one or more ring carbons is selected such that the macrocyclic ring has a ($\lambda\lambda\lambda\lambda$) orientation, then the tetraazacyclododecane ligand again has a capped twisted square antiprism configuration.

The following clerical or typographical errors were noted in Column 8, lines 61-67 through and including Column 9, lines 1-11:

In certain preferred embodiments of the method 100, the contrast agent further includes a carrier component, conjugated to one or more of the functionalized substituents R^6 , as discussed above. In certain embodiments of the present invention, the CA includes at least one and up to twenty of the tetraazacyclododecane ligands. Such ligands may be covalently or noncovalently bonded to a carrier component, such as described above, comprising a portion of the contrast agent. Collecting several such ligands, and associated metal ions and bound water molecules, allows a larger effective magnetic resonance signal to be achieved at lower concentrations of contrast agent. In certain such embodiments, where the water molecule (H_2O) associated with the tetraazacyclododecane ligand has a τ_M^{298} , of between about 10 and about 100 nanoseconds, the water molecule associated with a contrast agent that further includes a carrier component has a relativity relativity at 298°C , r_1^{298} , of at least about $50 \text{ mM}^{-1} \text{ s}^{-1}$.

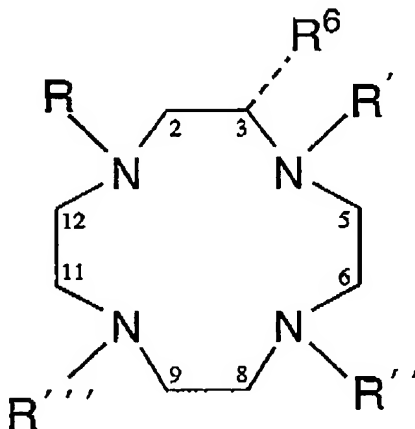
The following clerical or typographical errors were noted in Column 11, lines 59-67 through and including Column 12, lines 1-5:

The two complexes $[\text{Gd}(\text{S-RRRR-NO}_2\text{BnDOTMA})]^-$ and $[\text{Gd}(\text{s-ssss-NO}_2\text{BnDOTMA})]^-$ $[\text{Gd}(\text{S-SSSS-NO}_2\text{BnDOTMA})]^-$ have substantially different $1/T_2$ - temperature profiles, indicating substantially different water exchange rates. The profile for $[\text{Gd}(\text{S-RRRR-NO}_2\text{BnDOTMA})]^-$ $[\text{Gd}(\text{S-RRRR-NO}_2\text{BnDOTMA})]^-$, rises, maximizes and then falls away with increasing temperature, indicative of fairly slow water exchange. In contrast, the profile for $[\text{Gd}(\text{S-SSSS-NO}_2\text{BnDOTMA})]^-$, did not reach a maximum within the temperature range study, indicative of a more rapid water exchange. The values of τ_M^{298} obtained by fitting procedures, well known to those skilled in the art, to profiles such as depicted in FIGURE 4, are summarized in TABLE 2. Also shown in TABLE 2 are the relaxivities of water molecules associated with these ~~omers~~ isomers at 25 and 37 °C.

The following clerical or typographical error was noted in Claim 1:

1. A magnetic resonance contrast agent compound comprising:

a ~~tetraacyclododecane~~ tetraazacyclododecane ligand having a general structural formula as follows:



and comprising a ~~macrocycle~~ macrocyclic ring and wherein pendant arms R, R', R'' and R''' attached to a ring nitrogen have the general formula: $-\text{C}^*\text{HR}^1\text{R}^2$ and for three or more of said pendant arms a chirality of said carbon atoms C^* are identical for each of said three or more pendant arms, said R^1 are groups larger than hydrogen, and said R^2 is selected from the ~~group~~ group consisting of:

an alcohol ($-\text{CH}_2\text{OH}$);

amides ($-\text{CONR}^3\text{R}^4$, where R^3 and R^4 are organic groups);

a carboxylate ($-\text{COOH}$);

phosphinates ($-\text{PO}_2\text{HR}^5$, where R^5 is an organic group); and

a phosphonate ($-\text{PO}(\text{OH})_2$); and

wherein one or more of substituents R^6 is a group larger than a methyl group and is located on one or more ring carbons; and

a ~~paramagnetic~~ paramagnetic metal ion coordinated to said tetraazacyclododecane ligand.

The following clerical or typographical error was noted in Claim 5:

5. The magnetic resonance contrast agent compound as recited in Claim 1, wherein said chirality of said carbon atoms C' is controlled to provide said three or more of said pendant arms with a Δ or Λ orientation, and wherein a chirality of a ring carbon bonded to said one or more of substituents R^6 provides said ~~maereeylie~~ macrocyclic ring with an opposite orientation, $\lambda\lambda\lambda\lambda$ or $\delta\delta\delta\delta$, respectively, said tetraazacyclododecane ligand thereby having a monocapped square antiprism coordination geometry.

The following clerical or typographical error was noted in Claim 6:

6. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said ~~alcohol~~ alcohol or amide, and further including a water molecule associated with said tetraazacyclododecane ligand and said ~~paramagnetic~~ paramagnetic metal ion, said water molecule having a residence lifetime at about 298°K , τ_{M}^{298} , of ~~between~~ between about 10 and about 5000 microseconds.

The following clerical or typographical error was noted in Claim 7:

7. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said carboxyl, and further including a water molecule associated with said ~~tetreyelododecane~~ tetraazacyclododecane ligand and said paramagnetic metal ion, said water molecule having a residence lifetime at about 298°K , τ_{M}^{298} , of between about 100 and about 500 nanoseconds.

The following clerical or typographical error was noted in Claim 8:

8. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said phosphonate or said phosphinate, and further including a water molecule associated with said ~~tet-azacyclododecane~~ tetraazacyclododecane ligand and said paramagnetic metal ion, said water molecule having a residence ~~lifetime~~ lifetime at about 298°K , τ_M^{298} , of between about 10 and about 100 nanoseconds.

The following clerical or typographical error was noted in Claim 9:

9. The magnetic resonance contrast agent compound as recited in Claim 1, wherein said R^1 is a methyl group, said R^2 is said ~~carboxyl~~ carboxyl, and said R^6 is a para-aminobenzyl group and said paramagnetic metal ion is Gd^{3+} .

The following clerical or typographical error was noted in Claim 11:

11. The magnetic resonance contrast agent ~~compound~~ compound as recited in Claim 1, wherein at least one of said one or more of substituents R^6 include a functional group selected from the group consisting of:

amino groups;

carboxylates;

isothiocyanates; and

maleimides; and

a carrier component conjugated to said functional group.

Applicants respectfully request that a Certificate of Correction be issued pursuant to 37 C.F.R. §1.322. A Certificate of Correction reflecting these changes is enclosed. There is no fee associated with this correction since the errors listed above were made by the USPTO. However, the Commissioner is authorized to credit any overages or charge any additional fees in connection with this communication to Deposit Account Number 08-2395.

Respectfully submitted,

HITT GAINES, P.C.



Ronald J. Corbett

Registration No. 47,500

Date: August 10, 2006

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PTO/SB/44 (04-04)

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(Also Form PTO-1050)**UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION**

PATENT NO. : 7,012,140

DATED : March 14, 2006

INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4, lines 14-17 should appear as follows:

FIGURE 3A and FIGURE 3B illustrates exemplary ^1H NMR spectra of ~~$[\text{Eu}(\text{S-RRRR-NO}_2\text{BnDOTMA})]$~~ $[\text{Eu}(\text{S-RRRR-NO}_2\text{BnDOTMA})]$ and $[\text{Eu}(\text{S-SSSS-NO}_2\text{BnDOTMA})]$, respectively, produced according to the present; and

Column 5, lines 60-67 through and including Column 6, lines 1-3 should appear as follows:

For example, when the three or more pendant arm carbon atoms C' have Δ orientations and the chirality of the one or more R^6 -substituted ring carbons is selected such that the macrocyclic ring has an identical ($\delta\delta\delta\delta$) orientation, then the tetraazacyclododecane ligand has a capped twisted square antiprism configuration. Or, when the three or more pendant arm carbon atoms C' have Δ orientations and and the chirality of the one or more ring carbons is selected such that the macrocyclic ring has a ($\lambda\lambda\lambda\lambda$) orientation, then the tetraazacyclododecane ligand again has a capped twisted square antiprism configuration.

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PATENT NO. 7,012,140

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DATED : March 14, 2006

INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

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Column 8, lines 61-67 through Column 9, lines 1-11 should appear as follows:

In certain preferred embodiments of the method 100, the contrast agent further includes a carrier component, conjugated to one or more of the functionalized substituents R^6 , as discussed above. In certain embodiments of the present invention, the CA includes at least one and up to twenty of the tetraazacyclododecane ligands. Such ligands may be covalently or noncovalently bonded to a carrier component, such as described above, comprising a portion of the contrast agent. Collecting several such ligands, and associated metal ions and bound water molecules, allows a larger effective magnetic resonance signal to be achieved at lower concentrations of contrast agent. In certain such embodiments, where the water molecule (H_2O) associated with the tetraazacyclododecane ligand has a τ_M^{298} , of between about 10 and about 100 nanoseconds, the water molecule associated with a contrast agent that further includes a carrier component has a relativity relaxivity at $298^\circ C$, r_1^{298} , of at least about $50 \text{ mM}^{-1} \text{ s}^{-1}$.

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**UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION**

PATENT NO. : 7,012,140

DATED : March 14, 2006

INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 11, lines 59-67 through Column 12, lines 1-5 should appear as follows:

The two complexes $[Gd(S-RRRR-NO_2BnDOTMA)]^-$ and $[Gd(S-SSSS-NO_2BnDOTMA)]^-$ have substantially different $1/T_2$ - temperature profiles, indicating substantially different water exchange rates. The profile for $[Gd(S-RRRR-NO_2BnDOTMA)]^-$ rises, maximizes and then falls away with increasing temperature, indicative of fairly slow water exchange. In contrast, the profile for $[Gd(S-SSSS-NO_2BnDOTMA)]^-$, did not reach a maximum within the temperature range study, indicative of a more rapid water exchange. The values of τ_M^{298} obtained by fitting procedures, well known to those skilled in the art, to profiles such as depicted in FIGURE 4, are summarized in TABLE 2. Also shown in TABLE 2 are the relaxivities of water molecules associated with these ~~some~~ isomers at 25 and 37 °C.

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 7,012,140

DATED : March 14, 2006

INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

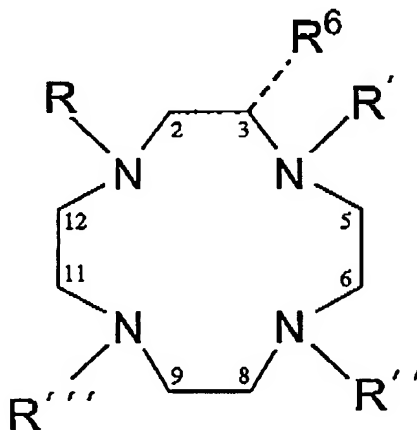
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1 should appear as follows:

The following clerical or typographical error was noted in Claim 1:

1. A magnetic resonance contrast agent compound comprising:

a ~~tetraacyclododecane~~ tetraazacyclododecane ligand having a general structural formula as follows:



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PATENT NO.

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 7,012,140

DATED : March 14, 2006

INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(claim 1 continued)

and comprising a ~~macroeylie~~ macrocyclic ring and wherein pendant arms R, R', R'' and R''' attached to a ring nitrogen have the general formula: $-C^*HR^1R^2$ and for three or more of said pendant arms a chirality of said carbon atoms C' are identical for each of said three or more pendant arms, said R¹ are groups larger than hydrogen, and said R² is selected from the group ~~group~~ consisting of:

an alcohol ($-CH_2OH$);

amides ($-CONR^3R^4$, where R³ and R⁴ are organic groups);

a carboxylate ($-COOH$);

phosphinates ($-PO_2HR^5$, where R⁵ is an organic group); and

a phosphonate ($-PO(OH)_2$); and

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DATED : March 14, 2006

INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(claim 1 concluded)

wherein one or more of substituents R^6 is a group larger than a methyl group and is located on one or more ring carbons; and

a ~~paramagnetic~~ paramagnetic metal ion coordinated to said tetraazacyclododecane ligand.

The correction to claim 1 is fully supported in Column 12, lines 48, 61 and 67 and Column 13, line 11.

Claim 5 should appear as follows:

5. The magnetic resonance contrast agent compound as recited in Claim 1, wherein said chirality of said carbon atoms C' is controlled to provide said three or more of said pendant arms with a Δ or Λ orientation, and wherein a chirality of a ring carbon bonded to said one or more of substituents R^6 provides said ~~macrocyclic~~ macrocyclic ring with an opposite orientation, $\lambda\lambda\lambda$ or $\delta\delta\delta$, respectively, said tetraazacyclododecane ligand thereby having a monocapped square antiprism coordination geometry.

The correction to claim 5 is fully supported in Column 13, line 41.

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INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 6 should appear as follows:

6. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said ~~alcohol~~ alcohol or amide, and further including a water molecule associated with said tetraazacyclododecane ligand and said ~~paramagnetic~~ paramagnetic metal ion, said water molecule having a residence lifetime at about 298°K, τ_M^{298} , of ~~between~~ between about 10 and about 5000 microseconds.

The correction to claim 6 is fully supported in Column 14, lines 2, 4, 5 and 6.

Claim 7 should appear as follows:

7. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said carboxyl, and further including a water molecule associated with said ~~tetrazacyclododecane~~ tetraazacyclododecane ligand and said paramagnetic metal ion, said water molecule having a residence lifetime at about 298°K, τ_M^{298} , of between about 100 and about 500 nanoseconds.

The correction to claim 7 is fully supported in Column 14, line 11.

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**UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION**

PATENT NO. : 7,012,140

DATED : March 14, 2006

INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 8 should appear as follows:

8. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said phosphonate or said phosphinate, and further including a water molecule associated with said ~~tet~~ tetra ~~azacyclododecane~~ azacyclododecane ligand and said paramagnetic metal ion, said water molecule having a residence ~~lifetime~~ lifetime at about 298°K , τ_M^{298} , of between about 10 and about 100 nanoseconds.

The correction to claim 8 is fully supported in Column 14, lines 18 and 20.

Claim 9 should appear as follows:

9. The magnetic resonance contrast agent compound as recited in Claim 1, wherein said R^1 is a methyl group, said R^2 is said ~~carboxyl~~ carboxyl, and said R^6 is a para-aminobenzyl group and said paramagnetic metal ion is Gd^{3+} .

The correction to claim 9 is fully supported in Column 14, line 24.

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PATENT NO. : 7,012,140

DATED : March 14, 2006

INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 11 should appear as follows:

11. The magnetic resonance contrast agent ~~compound~~ compound as recited in Claim 1, wherein at least one of said one or more of substituents R⁶ include a functional group selected from the group consisting of:

amino groups;

carboxylates;

isothiocyanates; and

maleimides; and

a carrier component conjugated to said functional group.

The correction to claim 11 is fully supported in Column 14, line 31.

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